Review of the PhD. Thesis by Tynchtyk Amatov entitled „New Thermal and Oxidative Radical Cyclization Methodology and Application to the Total Synthesis of Bridged Diketopirazine Alkaloids

The general aim of the Thesis is application of tandem radical reactions in natural product synthesis. The structure of the Thesis corresponds to that of research papers in the field, ie. individual chapters include Introduction, Aims, subchapters describing results and their discussion and Summary (conclusion). Experimental part and References follow up. According to WoS data, Mr. Amatov has been the first author of three papers in the highly prestigious *Angewandte Chemie Int. Ed.*; one of the papers is clearly related to the topic of the Thesis. The Thesis thus meets the criteria set by the Czech legislation as well as the requirements of Charles University.

The Thesis deals with total synthetic efforts towards dioxopiperazine alkaloids using tandem radical cyclizations as the key step. Given little progress in practical approach to the target molecules, the candidate chose an interesting, but extremely demanding aim.

The quallity and quantity of original research in a very demanding area of synthetic manipulation is outstanding. Overall results have again confirmed that in a total synthesis, the target is actually less important than what is found on the way. This is very well exemplified by the nice solvent-free procedure developed for the preparation of dioxopiperazines from dipeptides, which further opened the path to practical total syntheses of ardeemin and glyantripine. Initial attempts at effecting a tandem radical process failed, but the results showed that enolate oxidation was feasible. Hence, trapping the radical with TEMPO and subjecting the product to C-O bond thermal homolysis enabled the author to resolve the problem, and further evaluate the cyclizations of a variety of substrates with various unsaturated side chain structures including those attached via a heteroatom. Based on the data obtained, synthesis of a natural product analogue named 8-oxoasperparaline C and that of an advanced intermediate in the Williams´synthesis of bicyclomycin were accomplished. The results have again shown that having resolved the key step in a total synthesis is indeed important, but may mean very little, since the steps remaining to achieve the target tend to be no less challenging no matter how trivial they may seem. For example, it is no wonder that several different approaches for the buildup of the spirocyclic fragment of asperparaline C including the formation of two quaternary carbons had to be tested. The structures of the products have been thoroughly studied by multidimensional NMR and, in a number of instances, supported by X-ray data. Finally, Mr. Amatov has also studied an unusual *trans-cis* isomerization of dioxopiperazines, and described the kinetics of the process.

The Thesis is well written and logically guides the reader through the strategical and tactical development of the research. It is also written in good English, even though some typographical and factual errors could be found. However, none of them was serious enough to require correction (for example structures **2.34a** and **2.34b** are the same, but should be isomers).

I have the following points to be raised in a discussion:

1. The candidate could probably have been more careful in the depiction of stereocenters (or specify more carefully, which compounds were racemic). For example, structures **2.12** and **2.14** (Schemes 2.5 and 2.6) are depicted with one stereocenter of defined configuration, but the structures of the cyclization products (**2.2** and **2.3**) indicate loss of this stereochemical information during the lactamization step on SiO_2. Was it really so?
2. Pg. 50, according to Scheme 4.18, Fe^{II}-enolate **4.38** is hydrolyzed with MeOH to give **4.35** and (MeO)Fe^{I} species. How does reduction to Fe^{I} occur?
3. Pg. 55, the paragraph related to Scheme 4.24 is confusing, since it says that „…2:1 mixture of compounds was formed (Scheme 4.24). Their structure safely assigned…". However, Scheme 4.24 only shows that spirocycle **4.49** was not formed under the conditions given, and I have a feeling that whatever the products were, their structures were probably **not** safely assigned.

In summary, the work makes a very substantial contribution to knowledge, shows a good knowledge of the most recent literature, demonstrates the ability to conceive and execute excellent chemical research, and has then been reasonably well communicated. Therefore it provides clear evidence that the candidate is worthy of unconditional admission to the defence.

In Hradec Kralove 20. 5. 2016

Prof. Milan Pour